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Screening of conditionally reprogrammed patient-derived carcinoma cells identifies ERCC3-MYC interactions as a target in pancreatic cancer

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Abstract

©2016 AACR.Purpose: Even when diagnosed prior to metastasis, pancreatic ductal adenocarcinoma (PDAC) is a devastating malignancy with almost 90% lethality, emphasizing the need for new therapies optimally targeting the tumors of individual patients. Experimental Design: We first developed a panel of new physiologic models for study of PDAC, expanding surgical PDAC tumor samples in culture using short-term culture and conditional reprogramming with the Rho kinase inhibitor Y-27632, and creating matched patient-derived xenografts (PDX). These were evaluated for sensitivity to a large panel of clinical agents, and promising leads further evaluated mechanistically. Results: Only a small minority of tested agents was cytotoxic in minimally passaged PDAC cultures in vitro. Drugs interfering with protein turnover and transcription were among most cytotoxic. Among transcriptional repressors, triptolide, a covalent inhibitor of ERCC3, was most consistently effective in vitro and in vivo causing prolonged complete regression in multiple PDX models resistant to standard PDAC therapies. Importantly, triptolide showed superior activity in MYC-amplified PDX models and elicited rapid and profound depletion of the oncoprotein MYC, a transcriptional regulator. Expression of ERCC3 and MYC was interdependent in PDACs, and acquired resistance to triptolide depended on elevated ERCC3 and MYC expression. The Cancer Genome Atlas analysis indicates ERCC3 expression predicts poor prognosis, particularly in CDKN2A-null, highly proliferative tumors. Conclusions: This provides initial preclinical evidence for an essential role of MYC-ERCC3 interactions in PDAC, and suggests a new mechanistic approach for disruption of critical survival signaling in MYC-dependent cancers.

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